

What is claimed is:

1. An antibody that selectively binds to an epitope of HARE.
2. An antibody that selectively binds to an epitope of HARE and inhibits the binding of at least one of HA, chondroitin and chondroitin sulfate to HARE.
3. A humanized monoclonal antibody that selectively binds to an epitope of a HARE and inhibits the binding of at least one of HA, chondroitin and chondroitin sulfate to the HARE.
4. A method of making an antibody, comprising immunizing a non-human animal with an immunogenic fragment of HARE.
5. The method of claim 4 wherein the immunogenic fragment comprises a sequence in accordance with at least one of SEQ ID NO:2 and SEQ ID NO:25.
6. The method of claim 5 wherein the immunogenic fragment comprises a sequence in accordance with a portion of at least one of SEQ ID NO:2 and SEQ ID NO:25.
7. A method of making a humanized monoclonal antibody, comprising:

immunizing a non-human animal with an immunogenic fragment of HARE
to form a monoclonal antibody; and
removing portions of the monoclonal antibody which may be antigenic in a
human and substituting like portions of a human antibody therefor.

8. The method of claim 7 wherein the immunogenic fragment comprises a sequence in accordance with at least one of SEQ ID NO:2 and SEQ ID NO:25.

9. The method of claim 8 wherein the immunogenic fragment comprises a sequence in accordance with a portion of at least one of SEQ ID NO:2 and SEQ ID NO:25.

10. The method of claim 7 wherein the immunogenic fragment comprises an HA-binding domain of HARE.

11. A method of making an antibody, comprising the steps of:
identifying a hybridoma cell that produces a monoclonal antibody specific for HARE; and
culturing the hybridoma cell under conditions that permit production of the monoclonal antibody.

12. The method of claim 11 wherein the method further comprises isolating the monoclonal antibody from the cultured hybridoma cell.

13. A method of purifying a functionally active HARE wherein the HARE is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, comprising the steps of:

providing a biological sample containing HARE;

providing an affinity matrix comprising an antibody that selectively binds to an epitope of HARE and a solid support to which the antibody is bound;

contacting the biological sample with the affinity matrix such that HARE in the biological sample binds to the antibody of the affinity matrix;

separating the HARE bound to the antibody of the affinity matrix from the remainder of the biological sample; and

releasing the HARE from the antibody of the affinity matrix.

14. The method of claim 13 wherein, in the step of providing the biological sample, the biological sample is obtained from at least one of liver, spleen, lymph nodes and bone marrow.

15. The method of claim 13 wherein, in the step of providing an affinity matrix, the antibody of the affinity matrix inhibits the binding of at least one of HA, chondroitin and chondroitin sulfate to HARE.

16. The method of claim 13 wherein the step of releasing the HARE from the antibody of the affinity matrix is further defined as contacting the HARE bound to the antibody of the affinity matrix with an eluate which disrupts the binding between the HARE protein and the antibody.

17. The method of claim 13 wherein, in the step of providing an affinity matrix, the antibody of the affinity matrix is a monoclonal antibody.

18. A purified mammalian HARE comprising a polypeptide which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate.

19. A purified mammalian HARE comprising a protein having a molecular weight in a range of from about 175 kDa to about 190 kDa which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate.

20. The purified mammalian HARE of claim 19 wherein the HARE comprises a sequence in accordance with at least one of SEQ ID NO:2 and SEQ ID NO:25.

21. A purified mammalian HARE comprising a protein having a molecular weight in a range of from about 300 kDa to about 315 kDa which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, the protein comprising at least two disulfide-bonded subunits.

22. A purified mammalian HARE, comprising:

a protein which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, the protein being recognized by at least one of the monoclonal antibodies mAb-28, mAb-30, mAb-54, mAb-154, mAb-159, mAb-174, mAb-235, mAb-467, or a monoclonal antibody which demonstrates an immunological binding characteristic of such monoclonal antibodies.

23. The purified mammalian HARE of claim 22 wherein binding of at least one of the monoclonal antibodies to HARE results in inhibition of the ability of the protein to specifically bind at least one of HA, chondroitin and chondroitin sulfate.

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24. A purified mammalian HARE, comprising:

a protein which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, the protein comprising a sequence in accordance with SEQ ID NO:2.

25. A purified mammalian HARE, comprising:

a protein which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, the protein having at least 40% sequence identity to SEQ ID NO: 2.

26. The purified mammalian HARE of claim 25, wherein the protein has at least 80% sequence identity to SEQ ID NO:2.

27. The purified mammalian HARE of claim 25, wherein the protein has at least 90% sequence identity to SEQ ID NO:2.

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28. A purified mammalian HARE, comprising:

a protein which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, the protein comprising a sequence in accordance with SEQ ID NO:25.

29. A purified mammalian HARE, comprising:

a protein which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, the protein having at least 40% identity to SEQ ID NO: 25.

30. The purified mammalian HARE of claim 29, wherein the protein has at least 80% sequence identity to SEQ ID NO:25.

31. The purified mammalian HARE of claim 29, wherein the protein has at least 90% sequence identity to SEQ ID NO:25.

32. A purified mammalian HARE fragment, comprising:
a peptide which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, the peptide being recognized by at least one of the monoclonal antibodies mAb-28, mAb-30, mAb-54, mAb-154, mAb-159, mAb-174, mAb-235, mAb-467, or a monoclonal antibody which demonstrates an immunological binding characteristic of such monoclonal antibodies.

33. The purified mammalian HARE fragment of claim 32, wherein the peptide comprises a soluble fragment of HARE.

34. The purified mammalian HARE fragment of claim 33, wherein the peptide comprises an extracellular domain of HARE.

35. The purified mammalian HARE fragment of claim 33, wherein the peptide comprises an HA-binding domain of HARE.

36. The purified mammalian HARE fragment of claim 32, wherein binding of at least one of the monoclonal antibodies to the purified mammalian HARE fragment results in inhibition of the ability of the protein to specifically bind at least one of HA, chondroitin and chondroitin sulfate.

37. A purified mammalian HARE fragment, comprising:

a peptide which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, the peptide comprising a sequence in accordance with at least a portion of one of SEQ ID NO:2 and SEQ ID NO:25.

38. The purified mammalian HARE fragment of claim 37, wherein the peptide comprises a soluble fragment of HARE.

39. The purified mammalian HARE fragment of claim 38, wherein the peptide comprises an extracellular domain of HARE.

40. The purified mammalian HARE fragment of claim 38, wherein the peptide comprises an HA-binding domain of HARE.

41. A purified composition, wherein the purified composition comprises a functionally active HARE polypeptide.

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42. A purified composition, wherein the purified composition comprises a functionally active HARE polypeptide, wherein the functionally active HARE polypeptide has an amino acid sequence selected from the group consisting of an amino acid sequence in accordance with SEQ ID NO:2 and an amino acid sequence in accordance with SEQ ID NO:25.

43. A purified composition, comprising a polypeptide, wherein the polypeptide is a fragment of a functionally active HARE, the polypeptide able to bind at least one of HA, chondroitin and chondroitin sulfate.

44. The purified composition of claim 43, wherein the polypeptide comprises a soluble fragment of HARE.

45. The purified composition of claim 44, wherein the polypeptide comprises an extracellular domain of HARE.

46. The purified composition of claim 44, wherein the polypeptide comprises an HA-binding domain of HARE.

47. The purified composition of claim 43, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of at least a portion of the sequence in accordance with SEQ ID NO:2 and at least a portion of the sequence in accordance with SEQ ID NO:25.

48. A purified nucleic acid segment comprising a coding region encoding a functionally active HARE.

49. The purified nucleic acid segment of claim 48 wherein such purified nucleic acid segment comprises a nucleotide sequence in accordance with at least one of SEQ ID NO:1 and SEQ ID NO:24.

50. A purified nucleic acid segment having a coding region encoding a functionally active HARE, wherein the purified nucleic acid segment is capable of hybridizing to a nucleotide sequence complementary to at least one of the nucleotide sequences of SEQ ID NO:1 and SEQ ID NO:24.

51. The purified nucleic acid segment of claim 50 wherein the purified nucleic acid segment hybridizes to a nucleotide sequence complementary to at least one of the nucleotide sequences of SEQ ID NO:1 and SEQ ID NO:24 under stringent hybridization conditions.

52. The purified nucleic acid segment of claim 50 wherein the purified nucleic acid segment hybridizes to a nucleotide sequence complementary to at least one of the nucleotide sequences of SEQ ID NO:1 and SEQ ID NO:24 under relaxed hybridization conditions.

53. A purified nucleic acid segment having a coding region encoding a functionally active HARE, wherein the purified nucleic acid segment has semiconservative or conservative amino acid codon changes when compared to the nucleotide sequence of SEQ ID NO:1.

54. A purified nucleic acid segment having a coding region encoding a functionally active HARE, wherein the purified nucleic acid segment has semiconservative or conservative amino acid codon changes when compared to the nucleotide sequence of SEQ ID NO:24.

55. A recombinant vector selected from the group consisting of a plasmid, cosmid, phage, or virus vector and wherein the recombinant vector further comprises a purified nucleic acid segment having a coding region encoding a functionally active HARE.

56. The recombinant vector of claim 55, wherein the purified nucleic acid segment comprises a nucleotide sequence selected from the group consisting of a nucleotide sequence in accordance with SEQ ID NO:1 and a nucleotide sequence in accordance with SEQ ID NO:24.

57. The recombinant vector of claim 56, wherein the plasmid further comprises an expression vector.

58. The recombinant vector of claim 57, wherein the expression vector comprises a promoter operatively linked to the HARE coding region.

59. A recombinant host cell, comprising a recombinant vector containing a nucleic acid segment having a coding region encoding a functionally active HARE introduced into a host cell.

60. The recombinant host cell of claim 59 wherein the host cell comprises a eucaryotic cell.

61. The recombinant host cell of claim 59, wherein the nucleic acid segment comprises a nucleotide sequence selected from the group consisting of a nucleotide sequence in accordance with SEQ ID NO:1 and a nucleotide sequence in accordance with SEQ ID NO:24.

62. The recombinant host cell of claim 59, wherein the recombinant host cell produces a functionally active HARE which specifically binds and endocytoses at least one of HA, chondroitin and chondroitin sulfate.

63. The recombinant host cell of claim 59, wherein the recombinant vector is introduced into the host cell by a method selected from the group consisting of transfection, electroporation, transduction and combinations thereof.

64. The recombinant host cell of claim 59, wherein the purified nucleic acid segment is integrated into a chromosome of the recombinant host cell.

65. A method of producing a functionally active HARE wherein the HARE is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, the method comprising the steps of:

providing a recombinant host cell containing a recombinant DNA segment which encodes HARE and is capable of expressing a functionally active HARE;

culturing the recombinant host cell under conditions that allow for expression of the recombinant DNA segment encoding a functionally active HARE, thereby producing functionally active HARE; and separating and purifying the functionally active HARE from the recombinant host cell.

66. A method of producing a peptide which is able to specifically bind at least one of HA, chondroitin and chondroitin sulfate, the method comprising the steps of: providing a recombinant host cell containing a recombinant DNA segment which encodes the peptide; culturing the recombinant host cell under conditions that allow for expression of the recombinant DNA segment encoding the peptide, thereby producing the peptide; and separating and purifying the peptide from the recombinant host cell.

67. The method of claim 66 wherein the peptide comprises an HA-binding domain of HARE.

68. An isolated nucleic acid sequence encoding functionally active HARE, the nucleic acid sequence selected from the group consisting of:

- (a) a nucleic acid sequence in accordance with SEQ ID NO:1;
- (b) a nucleic acid sequence in accordance with SEQ ID NO:24;



- (c) a nucleic acid sequence complementary to the nucleic acid sequence in accordance with SEQ ID NO:1;
- (d) a nucleic acid sequence complementary to the nucleic acid sequence in accordance with SEQ ID NO:24;
- (e) a nucleic acid sequence which will hybridize to the nucleic acid sequence in accordance with SEQ ID NO:1 or a fragment thereof;
- (f) a nucleic acid sequence which will hybridize to the nucleic acid sequence in accordance with SEQ ID NO:24 or a fragment thereof;
- (g) a nucleic acid sequence which will hybridize to a nucleic acid sequence complementary to SEQ ID NO:1;
- (h) a nucleic acid sequence which will hybridize to a nucleic acid sequence complementary to SEQ ID NO:24;
- (i) a nucleic acid sequence which will hybridize to SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:6; and
- (j) nucleic acid sequences which but for the degeneracy of the genetic code, or encoding of functionally equivalent amino acids, would hybridize to one of the nucleic acid segments defined in (a), (b), (c) or (d).

69. A eucaryotic host cell transformed or transfected with the isolated nucleic acid sequence according to claim 53.

70. The eucaryotic host cell of claim 69, wherein the isolated nucleic acid sequence is integrated into a chromosome of the eucaryotic host cell.

71. A purified nucleic acid segment according to SEQ ID NO:3 capable of hybridizing to SEQ ID NO:1.

72. A purified nucleic acid segment according to SEQ ID NO:4 capable of hybridizing to SEQ ID NO:1.

73. A purified nucleic acid segment according to SEQ ID NO:5 capable of hybridizing to SEQ ID NO:24.

74. A purified nucleic acid segment according to SEQ ID NO:6 capable of hybridizing to SEQ ID NO:24.

75. A method of identifying compounds which inhibit binding of HA to HARE, comprising the steps of:

providing a purified fragment of HARE capable of binding HA;

forming a first affinity matrix comprising the purified fragment of HARE bound to a solid support;

contacting a test compound with the first affinity matrix to form a treated affinity matrix;

contacting HA with the first affinity matrix and contacting HA with the treated affinity matrix; and

determining that the test compound inhibits binding of HA to HARE when HA binds to a greater extent to the first affinity matrix than to the treated affinity matrix.

76. The method of claim 75 wherein, in the step of providing a purified fragment of HARE, the purified fragment of HARE comprises a soluble fragment of HARE.

77. The method of claim 75 wherein, in the step of providing a purified fragment of HARE, the purified fragment of HARE comprises an extracellular domain of HARE.

78. The method of claim 75 wherein, in the step of providing a purified fragment of HARE, the purified fragment of HARE comprises an HA-binding domain of HARE.

79. A method of identifying compounds which inhibit binding of at least one of chondroitin and chondroitin sulfate to HARE, comprising the steps of:

providing a purified fragment of HARE capable of binding at least one of chondroitin and chondroitin sulfate;

forming a first affinity matrix comprising the purified fragment of HARE bound to a solid support;

contacting a test compound with the first affinity matrix to form a treated affinity matrix;

contacting at least one of chondroitin and chondroitin sulfate with the first affinity matrix and contacting at least one of chondroitin and chondroitin sulfate with the treated affinity matrix; and

determining that the test compound inhibits binding of at least one of chondroitin and chondroitin sulfate to HARE when at least one of chondroitin and chondroitin sulfate binds to a greater extent to the first affinity matrix than to the treated affinity matrix.

80. The method of claim 79 wherein, in the step of providing a purified fragment of HARE, the purified fragment of HARE comprises a soluble fragment of HARE.

81. The method of claim 79 wherein, in the step of providing a purified fragment of HARE, the purified fragment of HARE comprises an extracellular domain of HARE.

82. The method of claim 79 wherein, in the step of providing a purified fragment of HARE, the purified fragment of HARE comprises an HA-binding domain of HARE.

83. A method of treating a liquid solution containing at least one of HA, chondroitin and chondroitin sulfate, comprising the steps of:

providing an affinity matrix comprising a functionally active fragment of HARE bound to a solid support; and

exposing a quantity of the liquid solution to the affinity matrix wherein at least one of HA, chondroitin and chondroitin sulfate contained in the liquid solution is removed therefrom.

84. The method of claim 83 wherein the liquid solution is blood or plasma.

85. The method of claim 83 wherein, in the step of providing an affinity matrix, the functionally active fragment of HARE comprises a soluble fragment of HARE.

86. The method of claim 83 wherein, in the step of providing an affinity matrix, the functionally active fragment of HARE comprises an extracellular domain of HARE.

87. The method of claim 83 wherein, in the step of providing an affinity matrix, the functionally active fragment of HARE comprises an HA-binding domain of HARE.

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